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10/657,851	09/09/2003	Christopher J. Murphy	TPLANT-08360	2123

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EXAMINER	
LIU, SAMUEL W	

ART UNIT	PAPER NUMBER
1656	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/657,851	MURPHY ET AL.	
	Examiner	Art Unit	
	SAMUEL W. LIU	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 September 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *53-64,66 and 67* is/are pending in the application.

4a) Of the above claim(s) *none* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *53-64 and 66-67* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of claims

Claims 53-64 and 66-67 are pending.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed 9/4/08 has been entered.

The amendment filed 9/4/08 which amends claims 53 and 66-67, and cancels claim 65 has been entered. Claims 1-52 were canceled by the amendment filed 1/16/08. Claims 53-64 and 66-67 are examined in this Office action.

Withdrawal of the rejection

The rejection of claims 53, 56, 59-60, 63 and 66 under 35USC 102 is withdrawn in light of the amendment of claims 53 and 66.

New- Claim Rejections - 35 USC §103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any

evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

[1] Claims 53-55, 60 and 66 are rejected under 35 U.S.C. 103(a) as being unpatentable over Petrinec et al. (*Surgery* (1996) 120, 221-225) in view of Steffen et al. (*Transplant Int.* (1990) 3, 133-136), and Tavakkol et al. *(Arch. Dermatol. Res.* (1999) 291, 643-651).

At abstract and page 222, lines 20-27, Petrinec et al. teach a preparation comprising (i) insulin-like growth factor (IGF-1) of concentration 10^{-7} mol/L (i.e., ~765 ng/ml based on that IGF-1 has molecular weight of 7649 daltons, see "*Discussion of art*" [7]) which has the activity of protecting organs (page 221, right column, last three lines), and thus, has potential for use in maintaining/preserving the functions of organs such as kidney (see abstract), (ii) an organ (e.g., kidney), and (iii) Euro-Collins organ preservation solution (EC-solution) (this solution does not contain lactobionate).

Yet, Petrinec et al. do not expressly teach that the "solution" comprises lactobionate nor that the IGF-1 concentration is within 1-100 ng/ml range.

Steffen et al. teach that "UW-solution" proved to be superior to "EC solution" (page 136, left column, second last paragraph, lines 1-2) for organ preservation are life-sustaining, wherein the "UW-solution" contains lactobionate (page 135, right column, last paragraph, lines 2-6) of concentration 100 mm/L, i.e., 100 mM ((see "*Discussion of art*" [1]).

The UW solution also comprises hydroxyethyl starch of 50 g/L (see "*Discussion of art*" [2]).

Tavakkol et al. teach that concentration of IGF-1 of 2 ng/ml up to 20 ng/ml which is

formulated in an organ culture composition (e.g., "KBM") (page 644, left column, section "*Organ culture protocol*"; page 646, right column, last paragraph, lines 4-5; and page 647, left column, lines 2-3).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to prepare the composition for organ preservation by substituting "EC solution" of Petrinec et al. with "UW solution" taught by Steffen et al. which comprises 100 mM lactobinate and 50 g/L hydroxyethyl starch, because the UW solution is superior to the EC-solution with advantages that the "EC solution" shows irreversible damage to the preserved organ cells while, in contrast, with the "UW solution", all preserved organ such as livers are life-sustaining, as taught by Steffen et al. (page 136, paragraphs 3-4). It would have been obvious to one of ordinary skill in the art at the time the invention was made to use the IGF-1 concentration of 2-20 ng/ml (falling in instant 1-100 ng/ml) range taught by Tavakkol et al. for preparing said composition. This is because the IGF-1 concentration of 10^{-7} mol/L (i.e., 765 ng/ml, see above) taught by primary reference Petrinec et al. is designated to be used in flush perfusion of organ in order for the organ storage (page 222, left column, line 28) rather than directly used in preservation of organ whereas the IGF-1 concentration (2-20 ng/ml) taught by Tavakkol et al. is particularly useful in the organ culture for human organ preservation (see page 644, left column, lines 4-6). Therefore, the combined teachings of Petrinec et al., Steffen et al. and Tavakkol et al. render obvious over instant in vitro composition comprising an internal organ, lactobionate of concentration range about 1-500 mM and IGF-1 of concentration range about 1-100 ng/ml, and hydroxyethyl starch of concentration range 1-200 g/l (claims 53, 54, 55, 60 and 66).

[2] Claims 56-59 are rejected under 35 U.S.C. 103(a) as being unpatentable over Petrinec et al. (*Surgery* (1996) 120, 221-225) in view of Steffen et al. (*Transplant Int.* (1990) 3, 133-136), Tavakkol et al. *(Arch. Dermatol. Res.* (1999) 291, 643-651) as applied to Claim 53, further in view of Janoff et al. (US Pat. No. 5766624) and Hancock et al. (US Pat. No. 6172185 B1).

The teachings of Petrinec et al. in view of Steffen et al. and Tavakkol et al. applicable to claim 53 have been discussed above.

Petrinec et al. et al. do not expressly teach that the composition further comprises antimicrobial peptide.

Janoff e al. teach antimicrobial peptide defensin (claims 56-57), e.g., indolicidin (col. 3, lines 23), has ability of not only inhibiting and preventing microbial infection or fungus infection (col. 3, line 65 to col. 4, line 7 and line 25), but also useful for organ transplantation (col. 4, lines 4-5) which includes organ preservation.

Hancock et al. teach a defensin peptide "RLSRIVVIRVCR" of SEQ ID NO:3 (see abstract) which has sequence identity to instant SEQ ID NO:37 (claim 58).

Also, at Table 8, col. 23, Janoff et al. teach working concentration of the defensin with range 0.5-2 mg/ml (using free defensin), as applied to claim 59.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to formulate the Petrinec's preparation with defensin peptide such as the defensin of "SEQ ID NO:3" taught by Hancock et al. which has been sequenced and well characterized for its antibacterial activity (col. 8, lines 52-57, and abstract). This is because Janoff et al. have taught the usefulness of the defensin peptides in the organ transplantation/preservation (see

above), and because of particular usefulness (see col. 4, lines 22-25) of defensin in treating animal afflicted with microbial infection (including both bacterial and fugues infections). Having been motivated by these advantages, one skilled in the art would have readily added the defensin peptide into the above discussed composition for microbes-free organ preservation with reasonably expected success.

[3]Claims 61-62 are rejected under 35 U.S.C. 103(a) as being unpatentable over Petrinec et al. (*Surgery* (1996) 120, 221-225) in view of Steffen et al. (*Transplant Int.* (1990) 3, 133-136), Tavakkol et al. *(Arch. Dermatol. Res.* (1999) 291, 643-651) as applied to Claim 53, further in view of and Nishida et al. (*J. Cell. Physiol.* (1996) 169, 159-166).

The teachings of Petrinec et al. in view of Steffen et al. and Tavakkol et al. as applied to claim 53 have been discussed above.

Yet, Petrinec et al. do not expressly teach the composition further comprises further comprises substance P.

Nishida et al. teach that substance P (SP) has synergistic effect with IGF-1 (see Fig. 8, page 164) and SP can stimulate cornea epithelial cell proliferation (see Fig. 7) as well as smooth muscle cells, fibroblast, endothelial cells and T-lymphocytes (page 165, left column, 3rd paragraph). SP can promote healing of epithelial defects in the eye (organ) (page 165, right column, last paragraph) wherein the "healing" is related to organ preservation process. Also, Nishida et al. teach working concentrations of SP of 10-50 μg/ml (see Fig. 7B, and page 162, right column, 3rd paragraph). Because IGF-1 is component of organ preservation composition,

and becasue SP is capable of synergy with/enhancing IGF-1, SP is a competent agent for the organ preservation composition.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to further formulate the Petrinec's preparation with SP.

This is because the SP synergistic effect with IGF-1 wherein it has been known in the art that IGF-1 is safe therapeutic agent for preventing delayed organ graft function in organ transplantation, e.g., renal transplantation without any significant adverse sequelae, and that the organ (e.g., kidney) preservation solution supplemented with IGF-1 exhibits less functional damage or organ injury, as taught by Petrinec et al. (page 221, right column, last four sentences, page 225; left column, last paragraph; and page 223, left column, lines 11-13). Thus, one skilled in the art would have added SP of 10-50 μg/ml (claims 61-62) as taught by Nishida et al. to the composition according to combination of teachings Petrinec et al., Steffen et al. and Tavakkol et al. discussed above with reasonably expected success.

[4] Claims 63-64 are rejected under 35 U.S.C. 103(a) as being unpatentable over Petrinec et al. (*Surgery* (1996) 120, 221-225) in view of Steffen et al. (*Transplant Int.* (1990) 3, 133-136), Tavakkol et al. *(Arch. Dermatol. Res.* (1999) 291, 643-651) as applied to Claim 53, further in view of Lambiase A. (US Pat. No. 6537808 B2).

The teachings of Petrinec et al. in view of Steffen et al. and Tavakkol et al. as applied to claim 53 have been discussed above.

Yet, Petrinec et al. et al. do not expressly teach the composition further comprises further comprises nerve growth factor (NGF).

Lambiase A. teach use of NGF for storage of organ cornea in culture (see abstract), and teach addition of NGF to said organ culture for obtaining the explanted organ thereof (col. 7, lines 1-3); wherein the NGF concentration is about 100 ng/ml (col. 7, line 7).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to further formulate the Petrinec's preparation with NGF of the concentration 100 ng/ml. This is also because NGF has ability of increasing the content of SP as taught by Nishida at al. (page 160, left column, lines 14-15); said "increase" has positive input on IGF-1 which in turn would have led to reducing organ tissue damage/injury during the organ preservation process. Thus, it would have been obvious for the ordinary artisan to try it out with reasonable expectation of success; i.e., incorporate NGF of 100 ng/ml (claims 63-64) to the composition according to combination of teachings Petrinec et al., Steffen et al. and Tavakkol et al. discussed above, so as to achieve desirable orange preservation and thereby better organ transplantation that is based on the preservation, as person of ordinary skill also is a person of ordinary creativity, not an automaton.

Therefore, the claimed invention was *prima facie* obvious to make and use the invention at the time it was made.

[5] Claim 67 is rejected under 35 U.S.C. 103(a) as being unpatentable over Petrinec et al. (*Surgery* (1996) 120, 221-225) in view of Steffen et al. (*Transplant Int.* (1990) 3, 133-136), Tavakkol et al. *(Arch. Dermatol. Res.* (1999) 291, 643-651), Nishida et al. (*J. Cell. Physiol.* (1996) 169, 159-166), and Lambiase A. (US Pat. No. 6537808 B2).

At abstract and page 222, lines 20-27, Petrinec et al. teach a preparation comprising (i)

insulin-like growth factor (IGF-1) of concentration 10^{-7} mol/L (i.e., ~765 ng/ml based on that IGF-1 has molecular weight of 7649 daltons, see "*Discussion of art*" [7]) which has the activity of protecting organs (page 221, right column, last three lines), and thus, has potential for use in maintaining/preserving the functions of organs such as kidney (see abstract), (ii) an organ (e.g., kidney), and (iii) Euro-Collins organ preservation solution (EC-solution) (this solution does not contain lactobionate).

Yet, Petrinec et al. do not expressly teach that the "solution" comprises lactobionate nor that the IGF-1 concentration is within 1-100 ng/ml range.

Steffen et al. teach that "UW-solution" proved to be superior to "EC solution" (page 136, left column, second last paragraph, lines 1-2) for organ preservation are life-sustaining, wherein the "UW-solution" contains lactobionate (page 135, right column, last paragraph, lines 2-6) of concentration 100 mm/L, i.e., 100 mM ((see "*Discussion of art*" [1]).

The UW solution also comprises hydroxyethyl starch of 50 g/L (see "*Discussion of art*" [2]).

Tavakkol et al. teach that concentration of IGF-1 of 2 ng/ml up to 20 ng/ml which is formulated in an organ culture composition (e.g., "KBM") (page 644, left column, section "*Organ culture protocol*"; page 646, right column, last paragraph, lines 4-5; and page 647, left column, lines 2-3).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to prepare the composition for organ preservation by substituting "EC solution" of Petrinec et al. with "UW solution" taught by Steffen et al. which comprises 100 mM lactobinate and 50 g/L hydroxyethyl starch, because the UW solution is superior to the EC-solution with

advantages that the "EC solution" shows irreversible damage to the preserved organ cells while, in contrast, with the "UW solution", all preserved organ such as livers are life-sustaining, as taught by Steffen et al. (page 136, paragraphs 3-4). It would have been obvious to one of ordinary skill in the art at the time the invention was made to use the IGF-1 concentration of 2-20 ng/ml (falling in instant 1-100 ng/ml) range taught by Tavakkol et al. for preparing said composition. This is because the IGF-1 concentration of 10^{-7} mol/L (i.e., 765 ng/ml, see above) taught by primary reference Petrinec et al. is designated to be used in flush perfusion of organ in order for the organ storage (page 222, left column, line 28) rather than directly used in preservation of organ whereas the IGF-1 concentration (2-20 ng/ml) taught by Tavakkol et al. is particularly useful in the organ culture for human organ preservation (see page 644, left column, lines 4-6). Therefore, the combined teachings of Petrinec et al., Steffen et al. and Tavakkol et al. render obvious over in vitro composition comprising an internal organ, lactobionate of concentration range about 1-500 mM and IGF-1 of concentration range about 1-100 ng/ml, and hydroxyethyl starch of concentration range 1-200 g/l (claims 53, 54, 55, 60 and 66).

Yet, the above references do no expressly teach that the composition further comprises Nerve Growth Factor (NGF) and substance P.

Lambiase A. teach use of NGF for storage of organ cornea in culture (see abstract), and teach addition of NGF to said organ culture for obtaining the explanted organ thereof (col. 7, lines 1-3); wherein the NGF concentration is about 100 ng/ml (col. 7, line 7).

Nishida et al. teach that substance P (SP) has synergistic effect with IGF-1 (see Fig. 8, page 164) and SP can stimulate cornea epithelial cell proliferation (see Fig. 7) as well as smooth muscle cells, fibroblast, endothelial cells and T-lymphocytes (page 165, left column, 3rd

paragraph). SP can promote healing of epithelial defects in the eye (organ) (page 165, right column, last paragraph) wherein the "healing" is related to organ preservation process. Also, Nishida et al. teach working concentrations of SP of 10-50 μg/ml (see Fig. 7B, and page 162, right column, 3rd paragraph). Because IGF-1 is component of organ preservation composition, and becasue SP is capable of synergy with/enhancing IGF-1, SP is a competent agent for he organ preservation composition.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to further formulate the Petrinec's preparation with NGF and of the concentration 100 ng/ml, and substance P of 0.1-100 μg/ml concentration range because of the reasons below.

(**1**) NGF has ability of increasing the content of SP as taught by Nishida at al. (page 160, left column, lines 14-15); said "increase" has positive input on IGF-1 which in turn would have led to reducing organ tissue damage/injury during the organ preservation process. Thus, it would have been obvious for the ordinary artisan to try it out with reasonable expectation of success; i.e., incorporate NGF of 100 ng/ml (claims 63-64) to the composition according to combination of teachings Petrinec et al., Steffen et al. and Tavakkol et al.

(**2**) The SP synergistic effect with IGF-1 wherein it has been known in the art that IGF-1 is safe therapeutic agent for preventing delayed organ graft function in organ transplantation, e.g., renal transplantation without any significant adverse sequelae, and that the organ (e.g., kidney) preservation solution supplemented with IGF-1 exhibits less functional damage or organ injury, as taught by Petrinec et al. (page 221, right column, last four sentences, page 225; left column, last paragraph; and page 223, left column, lines 11-13). Thus, one skilled in the art would have

added SP of 10-50 μg/ml (claims 61-62) as taught by Nishida et al. to the composition with reasonably expected success.

Therefore, the combination of the above references' teachings renders the in vitro composition of claim 67 obvious.

Conclusion

No claims are allowed.

Discussion of the art

The prior art made of record and not currently relied upon in any rejections is considered pertinent to Applicants' disclosure:

[1] Hoenicke et al. (*J. Thorac Cardiovasc. Surg.* (2000) 120, 746-754) teach the lactobionate in the UW solution is 100 mmol/L (page 752, left column, 1st paragraph, line 13), i.e., 100 mM.

[2] Chien et al. (*J. Thorac Cardiovasc. Surg.* (2000) 119, 921-930) teach the UW solution comprises hydroxyethyl starch of 5 g/dl equivalent to 50 g/L (see Table I at page 922).

[3] McAnulty et al. (*Am. J. Transplan.* (2002) 2, 712-718) teach a kidney preservation composition, "TFS-UW" solution, comprising IGF-1 of 10 μg/L, i.e., 10 ng/ml, lactobionate (page 713, left column, last paragraph), and nerve growth factor and substance P (see abstract). Yet, this reference is not considered to be the prior art because it does not antedate the instant claims.

[4] Caverzasio et al. (*Kidney Intern.* (1995) 48, 33-38) teach that the IGF-1 plasma level in kidney organ is about 100 ng/ml (see Table 2, page 37) which is unaffected neither by protein intake nor by the PTH status (see abstract).

[5] Ortiz et al. (*Kidney Intern.* (2000) 58, 1632-1640) teach that vascular volume of the kidney is approximately 20% of the kidney volume (see Fig. 2, page 1636).

[6] Churchill et al. (US Pat. No. 5834178) teach a composition containing a kidney organ and the flush storage solution during flushing with said solution and stored in the same solution (see col. 7, lines 37-42). Said solution comprises lactobionate in a amount greater than 100 mM, and wherein blood vessel of the kidney inherently comprises IGF-1 having the plasma level about 100 ng/ml (see "*Discussion of art*" [4]). Considering that vascular volume of the kidney is approximately 20% of the kidney volume (see "*Discussion of art*" [5]); and considering that the flush storage solution is in the vascular dimension; and further, given that weight of kidney "*mg*" is considered to be approximately equal to kidney volume unit "*ml*"; then, the IGF-1 plasma concentration would be 20% × 1000 ng/ml = 20 ng/ml of total the organ volume. The Churchill et al. patent is no considered to be obviousness or anticipatory prior art against instant claim 53 because the above-discussed "blood vessel of the kidney" is not considered to be in vitro organ but in vivo organ, and because claim 53 recites "in vitro composition" wherein the "internal organ" (line 2 of claim 53) is an in vitro organ.

[7] Illi, O.E. (US Pat. No. 6214008 B1) teaches that IGF-1 has molecular weight of 7649 daltons (col. 3, lines 10-13).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Samuel Wei Liu whose telephone number is 571-272-0949. The examiner can normally be reached from 9:00 a.m. to 5:00 p.m. on weekdays. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr Bragton, can be reached on (571) 272-0931. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

/Samuel W Liu/Ph.D./
Examiner, Art Unit 1656
October 21, 2008

/Karen Cochrane Carlson/
Primary Examiner, Art Unit 1656